REMARKS

Claim amendments

Claim 10 has been amended to remove the language directed to the non-elected invention and to more clearly indicate that the boosting composition comprises a replication-deficient adenoviral vector including nucleic acid encoding said antigen or epitope operably linked to regulatory sequences whereby said antigen or epitope is expressed in the individual. Support for the amendment can be found, for example, on page 10, lines 22-26 of the specification.

No new matter has been added.

Election/Restrictions

The Examiner acknowledges that Applicants' traversal "is on the ground(s) that all three of the groups outlined in the restriction requirement are drawn to 'heterologous prime-boost' which is not disclosed by Kazanji et al" (Office Action, page 2). However, the Examiner does not find the traversal persuasive because "Kazanji disclose the administration of naked DNA plasmids containing the HTLV-1-*env* gene as the 'primer' and the administration of Ad5 containing the HTLV-1-*env gp46* gene as the 'booster'" and "[s]ince the genes administered in the 'prime' and the 'booster' are different and the form of said compositions are different . . . , said compositions are deemed to be heterologous to one another" (Office Action, page 2). The Examiner states that the "requirement is still deemed proper" and made final (Office Action, page 2).

Applicants respectfully disagree. Accordingly, Applicants are filing a Petition From Requirement For Restriction Under 37 C.F.R. §1.144 concurrently.

Oath/Declaration

The Examiner states that the declaration is defective because "[n]on-initialed and/or non-dated alterations have been made to the oath or declaration" (Office Action, page 3).

Applicants are filing a new Declaration in compliance with 37 C.F.R.§ 1.67(a) concurrently.

Specification

The Examiner states that the "use of the trademark Biorejector has been noted in the application" and "should be capitalized wherever it appears and be accompanied by the generic terminology" (Office Action, page 3).

The specification has been amended in accordance with the Examiner's request.

Objection to Claims 10-13 and 17-21

The Examiner has objected to Claims 10-13 and 17-21 because Claim 10, from which Claims 11-12 and 17-21 depend, recites limitations drawn to non-elected inventions" (Office Action, page 3). The Examiner states that "Claim 10 recites limitations drawn to non-elected inventions" and "Claims 11-13 and 17-21 are included in the objection as they depend from claim 10" (Office Action, page 3).

Claim 10 has been amended to delete the language directed to non-elected inventions, thereby obviating the objection.

Provisional Rejection of Claims 10, 11 and 18 under judicially created doctrine of double patenting

Claims 10, 11 and 18 are provisionally rejected under the judicially created doctrine of double patenting "as being unpatentable over claim 1 of copending Application No. 10/686,943" (Office Action, page 4).

Applicants will address the provisional obviousness-type double patenting rejection upon an indication that there is allowable subject matter in the subject application.

Rejection of Claims 10-13 and 17-21 under 35 U.S.C. §112, second paragraph

Claims 10-13 and 17-21 are rejected under 35 U.S.C. §112, second paragraph "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention" (Office Action, page 5). The Examiner states that Claim 10 "is rendered vague and indefinite by the use of the phrase 'nucleic acid encoding said antigen or

epitope operably linked to regulatory sequences for the production of said antigen or epitope in the individual by expression from the nucleic acid'" (Office Action, page 5).

Claim 10 has been amended to more clearly indicate that the boosting composition comprises a replication-deficient adenoviral vector including nucleic acid encoding said antigen or epitope operably linked to regulatory sequences whereby said antigen or epitope is expressed in the individual.

Rejection of Claims 10-13 and 17-21 under 35 U.S.C. §103(a)

Claims 10-13 and 17-21 are rejected under 35 U.S.C. §103(a) "as being unpatentable over McMichael et al (WO 98/56919) and Kazanji et al. (International Journal of Cancer, 1997, Vol. 71, pages 300-307 – IDS filed on 3-21-2002)" (Office Action, page 6). The Examiner states that McMichael *et al.* "disclose methods of inducing a CD8 T cell immune response comprising the administration of a priming composition and a boosting wherein said boosting composition comprises a non-replicating or replication impaired pox virus vector"; that "the priming composition can comprise a nucleic acid . . . . that is packaged in free form . . . Ty-VLP or a recombinant adenovirus"; that "the MVA can be used . . . in both the priming and boosting compositions . . . and that a variety of viral vectors . . . can be used in the priming composition" (Office Action, page 6). The Examiner notes that McMichael *et al.* "do not explicitly disclose the use of boosting compositions comprising non-replicating or replication impaired adenovirus vectors" (Office Action, page 6). The Examiner cites Kazanji *et al.* as disclosing "the administration of naked DNA plasmids containing the HTLV-1-*env* gene as the 'primer' and the administration of Ad5 containing the HTLV-1-*env gp46* gene as the 'booster'" and that "adenovirus vectors have the potential for oral immunization, are cheaply produced and have been successfully used in vaccines against EBV" (Office Action, pages 6-7). The Examiner concludes that "it would have been obvious for one of ordinary skill in the art at the time the invention was made to use the adenovirus disclosed by Kazanji et al. in the compositions and methods disclosed by McMichael et al. in order to take advantage of the ability of the adenovirus vectors to be orally administered and to be cheaply made" and "[o]ne would have had a reasonable expectation of success as adenovirus vectors have been successfully used in other vaccine compositions and in prime-boost methodologies" (Office Action, page 7).

Applicants respectfully disagree. Where the claimed invention is rejected as obvious in view of a combination of references, §103 requires both (1) that "the prior art would have suggested to the person of ordinary skill in the art that they should . . . carry out the claimed process"; and (2) that the prior art should establish a reasonable expectation of success (In re Vaeck, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991)). "Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure." Id.

McMichael *et al.* disclose methods of generating a CD8+ T cell response against a target antigen comprising administering a priming composition comprising a source of one or more CD8+ T cell epitopes of the target antigen, together with a carrier, and a boosting composition comprising a source of one or more CD8+ T cell epitopes of the target antigen, including at least one CD8+ T cell epitope which is the same as a CD8+ T cell epitope of the priming composition, wherein the source of CD8+ T cell epitopes is a non-replicating or replication-impaired recombinant poxvirus vector with the proviso that if the source of epitopes in the priming composition is a viral vector, the viral vector of the boosting composition is derived from a different virus (McMichael *et al.*, page 10, lines 6-24).

Kazanji *et al.* tested immunization regimens against human T-cell leukemia virus type 1 (HTLV-1) in rats using recombinant adenovirus 5 vectors, naked DNA plasmid vectors or vaccinia virus vectors containing the HTLV-1-*env* gene. The "vaccination protocols using different vectors are shown in Table I (A, B and C)" of the Kazanji *et al.* reference (Kazanji *et al.*, column 1, under the heading "Animals, vaccination regimens and challenges with HTLV-1"). For the regimen utilizing the adenoviral vectors, Kazanji *et al.* either used an Ad5-HTLV-1-env for priming and an Ad5-HTLV-1-gp46 or recombinant gp46 protein for boosting (Kazanji *et al.*, page 301,Table IA). For the regimen utilizing the naked DNA plasmids, Kazanji *et al.* either used the naked DNA expression vector pMLP-HTLV-1-env for priming and a naked DNA expression vector pMLP-HTLV-1-gp46 or recombinant gp46 protein for boosting (Kazanji *et al.*, page 301, Table IB). However, Kazanji *et al.* do not disclose an immunization regimen which involved "the administration of naked DNA plasmids containing the HTLV-1-*env* gene as the 'primer' and the administration of Ad5 containing the HTLV-1-*env gp46* gene as the 'booster'" (Office Action, pages 6-7). As disclosed in Table IA of the Kazanji *et al.* reference, for the

immunization in which the adenoviral vector is used as the boosting composition, the priming composition is also an adenoviral vector.

Furthermore, Kazanji *et al.* teach that the "results presented in Figure 4 show that CTL were detected to the same extent in rats immunized with either Ad5-HTLV-1-*env* or pMLP-HTLV-1-*env*, and that the nature of the boosting with gp46 or Ad5-HTLV-1-*gp46* or pMLP-HTLV-1-*gp46* did not change the level of the response" (Kazanji *et al.*, page 303, columns 1-2, emphasis added). Thus, Kazanji *et al.* teach that boosting with adenovirus has roughly the same effectiveness as boosting with DNA (Kazanji *et al.*, Figures 4A, 4B). McMichael *et al.* show that DNA is not as effective a boosting agent as MVA in their heterologous prime boost method (McMichael, page 32, Table 4). Thus, based on the combined teachings of McMichael *et al.* and Kazanji *et al.*, one of skill in the art would not be motivated to substitute the non-replicating or replication-impaired recombinant poxvirus vector of McMichael *et al.* with the adenoviral vector and/or DNA plasmid of Kazanji *et al.* to induce an immune response.

In discussing obviousness, the court has stated that "[a]n invention is not obvious merely because it is a combination of old elements each of which was well known in the art at the time the invention was made. . . Rather, if such a combination is novel, the issue is whether bringing them together as taught by the patentee was obvious in light of the prior art. . . The critical inquiry is whether 'there is something in the prior art as a whole to suggest the desirability, and thus obviousness of making the invention'" (Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.13 USPQ2d 1737 at 1765). There is nothing in the McMichael *et al.* reference and/or the Kazanji *et al.* reference as a whole to suggest the desirability, and thus obviousness of using the adenovirus vector of Kazanji *et al.* in the heterologous prime boost method of McMichael *et al.*

The prior art combination of record has been made with the advantage of impermissible hindsight, and thus, the rejection is legally improper. That is, in making the obviousness rejection, the Examiner has read the prior art with the benefit of Applicant's disclosure in which there is a clear teaching of the desirability of administering a replication-deficient adenoviral vector encoding an antigen, to boost an immune response to the antigen in an individual, where the individual was previously primed with a heterologous composition. As the court made clear in In re Dow, it is not legally correct to rely on Applicant's disclosure for the suggestion that the cited references should be combined and the expectation of success (In re Dow Chemical, 5

U.S.P.Q.2d 1529, 1531-1532 (Fed. Cir. 1988)). In the present case, the suggestion or motivation for combining the references and the expectation of success are not found in the prior art, but rather in Applicant's disclosure.

The combined teaching of McMichael *et al.* and Kazanji *et al.* do not render obvious Applicants' claimed invention.

Rejection of Claims 10-13 and 17-21 under 35 U.S.C. §103(a)

Claims 10-13 and 17-21 are rejected under 35 U.S.C. §103(a) "as being unpatentable over McMichael et al (WO 98/56919) and Natuk et al., 1993, AIDS Research and Human Retroviruses, Vol. 9 No 5, pages 395-404 – IDS filed on 3-21-2002)" (Office Action, page 7). The Examiner cites McMichael *et al.* as above and cites Natuk *et al.* as disclosing "the use of vaccines comprising recombinant adenoviral vectors in prime-boost protocols" . . . and that "human adenoviruses possess significant advantages as vectors for recombinant vaccines including a strong safety record and multiple serotypes that can be exploited as vectors for booster immunizations" (Office Action, page 8). The Examiner concludes that "it would have been obvious for one of ordinary skill in the art at the time the invention was made to use the adenovirus disclosed by Natuk et al. in the compositions and methods disclosed by McMichael et al. in order to take advantage of the safety and versatility associated with adenovirus vectors" and "[o]ne would have had a reasonable expectation of success as adenovirus vectors have been successfully used in vaccines for the prevention of acute respiratory disease" (Office Action, page 8).

Applicants respectfully disagree. The teachings of McMichael *et al.* has been discussed above. Natuk *et al.* tested "[r]ecombinant human adenovirus (Ad) type -4, 5-, and 7-vectored vaccines expressing either the HIV *env* or *gag*-protease genes" for immunogenicity in chimpanzees (Natuk *et al.*, abstract). Natuk *et al.* teach a first phase of the vaccination protocol which consisted of "a primary and two booster immunizations with Ad-HIVs by the oral route of administration, followed by a single booster immunization with Gag and/or Env subunit vaccines" (Natuk *et al.*, abstract). However, Natuk *et al.* describe the use of replicating adenoviral vectors, which were detected in the chimpanzees following immunization (Natuk *et al.*, page 397, column 2).

McMichael *et al.* teach away from the use of replicating vectors in their heterologous prime boost method. Specifically, McMichael *et al.* find that "the greatest immunogenicity and protective efficiency is surprisingly observed with non-replicating vectors. The latter have an added advantage for vaccination in that they are in general safer for use in humans than replicating vectors" (McMichael *et al.*, page 10, lines 1-5).

Thus, the combined teaching of McMichael *et al.* and Natuk *et al.* do not render Applicants' claimed invention obvious.

Second Supplemental Information Disclosure Statement

A Second Supplemental Information Disclosure Statement (IDS) is being filed concurrently herewith. Entry of the IDS is respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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